Metabolic Consequences of Citrate
Marlies Ostermann, MD

Speaker 1:	00:00	Okay. Thank you. And it's my privilege to invite our third speaker who's Marlies Ostermann who got her MD from University of London and her PhD from Germany and she's been a consultant at Guy's Hospital in London for the last 15 years or so. Is that right?
Speaker 2:	00:17	That is correct.
Speaker 1:	00:19	and co-founder of the London AKI network.
Speaker 2:	00:20	Thank you very much. Thank you professor Ward, and, Professor Goldstein, for chairing this important symposium and thank you to all of you for being here. I also like to thank Matthieu and Ashita because they set the scene for me so it's relatively easy for me now to point out a few potential complications or consequences of citrate. like, Ashita I learned about citrate at this meeting. I had never used citrate until about 10 years ago and came to this meeting heard a lot about citrate, listened to one of Ahita's talks and essentially came back. In the UK at the time nobody was using citrate and after quite a battle within the hospital, it took some conviction in the department. We started using citrate. Now we were fortunate because by the time we came round to using citrate, a commercially available solutions were available protocols, thanks to professor Ward and to Ashita who had developed them. And so it was much, much easier for us. And so we were able to use a machine which had integrated software and had, obviously commercialized solutions. So over time, clearly citrate has become much easier and it's less complex, but I put it to you. There are still some metabolic consequences you need to be aware of. And Professor Legrand made a very good case highlighting the potential problem of metabolic alkalosis and alluded to the fact that this can be corrected relatively easy.
Speaker 2:	02:13	So in the next 20 minutes, I shall focus on another acid base disorder, mainly metabolic acidosis. I will also briefly talk about calories and, the provision of some calories through citrate and finish with some potential effects on bone metabolism. This is the Krebs cycle and I illustrate it here to show to you that we all have citrate. The citrate isn't anything foreign. We all have citrate in our body because citrate forms an important component of the Krebs cycle. We need citrate to generate energy in our mitochondria.

Speaker 2:	03:00	Now as professor Tolwani said normally our own citrate concentration is very low. she's already mentioned half of it is low and the systemic concentration is fairly, is very low. We're not at risk of bleeding to death because you need a much higher concentration in the blood to increase the bleeding time to infinity.
Speaker 2:	03:27	So we are safe. However, if we give and use citrate based anticoagulation, then obviously some of these, citrate will be removed through the filter, but a proportion of citrate and calcium will enter the systemic circulation.
Speaker 2:	03:46	Now the calcium and citrate wIll then be split again, calcium gets recycled and you use it again, which is great, and the citrate will get used as you would normally use it. We have a lot of citrate, as I've said, many in our bones, and it gets the extra citrate now gets slotted into the Krebs cycle as normal. Now, the Krebs cycle here is to metabolize citrate. It's particularly relevant, and the main source, and the main organs where citric gets metabolized is the liver and the skeletal muscle. Well, we have plenty of liver capacity to deal with extra citrate. We have enough when we have so many, so much muscle, but again, the muscle metabolism of muscle bulk will help metabolizing extra citrate.
Speaker 2:	04:41	Of note, waste Krebs cycle is oxygen dependent. We all know that, but it also means the metabolism of citrate is oxygen dependent. And it's important to keep in mind. Now my role was to talk about some metabolic consequences. Now, professor Legrand spent time talking about metabolic alkalosis. So I will not talk about that. But clearly that's a potential complication, which can be easily managed.
Speaker 2:	05:17	In Berlin, at the CRRT where they developed a particular citrate protocol, which is slightly different, but it's very similar to the other protocols which were talked about earlier. The experts looked at the risk of metabolic complications. I'm trying to establish how safe or unsafe is citrate actually and the concerns about acid-based disorders. Are they valid? For this reason they retrospectively analyzed an existing database which contained all the patients who has had citrate based CRRT, predominantly CVV HD during a 3 year period. As I said this, the most majority of patients were treated with continuous renal hemodialysis by use a 4% trisodium citrate. by use the commercially available, solutions and they have a clear protocol which essentially, asks the bedside staff, the nursing staff to aim for post filter ionized calcium concentration between 0.25 to 0.35 by adjusting the citrate supply and to adjust the calcium supplementation so

		that the systemic ionized calcium concentration is always maintained in the normal physiologic range.
Speaker 2:	06:54	It's very well established run by the nursing staff at the bedside and therefore they feel very comfortable that there are no problems with their protocol, but just quite important and it's a very, clear way. It's a standardized way of how it's delivered.
Speaker 2:	07:15	When they analyze the database as shown here, they saw that only around 3% of patients who fulfilled criteria of possible citrate accumulation based on the total ionized calcium concentration. And we looked quite hard, but there weren't really any more. It was -------% but it was lower than expected. Well, the question is, can you identify these patients? is there anything special about them? And why did these 3% of patients have problems, potentially developing citrate accumulation?
Speaker 2:	07:59	Well, when they looked at them in detail, it turned out, but all 32 patients, had severe shock with multiorgan failure, they were all on vasopressors. They were all on the ventilator. And although you may think maybe they just have all had liver failure actually turned out, but only a third of them are known to have liver dysfunction and the others as far as we can judge by that routinely measured liver enzymes, had adequate liver function. Well, what's interesting was that, they were all characterized by very high lactate level, which was in the range of around 15. And as you can get a good sense for this type of patients you wouldn't be surprised to hear that they all died. So the patients in this experienced citrate unit, still had problems they were characterized by the fact that they had multiorgan failure, which rendered them to citrate accumulation.
Speaker 2:	09:12	The team tried to establish whether they could just use a lactate of 15 as a potential cutoff to say, the lactate is 15, you should not have citrate. Because clearly in this group of patients, there was a such a high risk of mortality. But actually in the group of patients who didn't turn out to have citrate accumulation, they were also a large number of patients who at the time of citrate was started already had a lactate of 15 but were they on a positive trajectory and subsequently managed to metabolize citrate, So just a single value of a particular lactate level is not sufficient to identify those who subsequently developed citrate accumulation.
Speaker 2:	09:57	So the conclusion of this analysis where the aim was to find triggers to predict who would develop citrate accumulation, essentially was unsuccessful they were not able to identify those patients who were at highest risk of developing severe

		metabolic acidosis or worsening of metabolic acidosis as a result of citralte accumulation. All they could say was, but there is a proportion of patients characterized by being very sick and having signs of mitochondrial failure of intracellular hypoxia who may not tolerate citrate. And this is obviously explained by the fact that the Krebs cycle is oxygen dependent. So the first, serious metabolic complication of citrate could be worsening of metabolic acidosis in those who are unable to metabolize citrate as a result of intracellular hypoxia. Metabolic alkalosis. I won't talk any more about because professor Legrand talked about it much better than I ever could. The next potential metabolic consequence is caloric gain. And this comes up quite frequently, certainly in the unit where I work where people mention it and the dietitians talk about it.
Speaker 2:	11:27	There's no doubt that' citrate contributes to the caloric delivery. if so 1 mmol of citrate generates a caloric gain of around 2.5 kilojoule. Our question is this is a lot? Or is it a little? If you compare it with glucose, it's a little bit less than a mmol glucose. And the next question is how much is it, how much does it actually contribute to the overall caloric supply? And the literature varies and clearly it varies depending on which citrate formulation you use, how much citrate ACD-A systemic circulation and what protocol you're using.
Speaker 2:	12:13	Professor Kashani from the Mayo Clinic tried to shine a bit of light on this given that there was a lot of uncertainty and people were worried, but nobody really knew exactly how much calories and on whether this was actually an important problem in clinical practice. And in their, detailed at small patient populations of 10 patients who then got analyzed in detail, they established, but the,
New Speaker:	12:39	net caloric gain from citrate with a protocol they were using and using ACD-A citrate, resulted in a caloric gain of around 200, 250 kilo calories per day. So I take back from that, it's about half a mass spot in the UK. And you may say, well, is that bad? And with this, is it bad for a critically ill patient to get a bit of extra calories and extra mass by given that nutrition is a problem in critically ill patients, malnutrition is a problem, absorption is a problem. So I used to think this was not really a problem and I used to not completely ignore it, but I was never too worried about the caloric gain because I was much more worried about patients getting sufficient nutrition.
Speaker 2:	13:27	But it turns out that we should, or maybe I should be a little bit more concerned because we've learned through various nutrition studies, that overfeeding is not good it is potentially

harmful. So this is just one of the studies which led to this conclusion where they, retrospectively analyzed the relationship between energy administration or energy supply and outcome. And as you can see here, clearly overfeeding is bad and underfeeding is bad. So people who don't get enough calories have a higher mortality and people who get too much energy or too many calories are also at higher risk of dying. You would've thought that somehow if you achieved or delivered exactly what patients needed. So how a 100% delivery of the requirement that this was optimal. But it turned out that actually the optimal spot was in the hypocaloric field and delivering a little bit less than patients needed based on energy and requirement estimates was associated with the lowest mortality and they did some sub analysis looking at all patients or the long stay patients, but it always turned out the spot was in the first week was around 70 to 75%.

Speaker 2: 15:01

So given these results and others iin the literature, and it's not surprising that the latest nutrition guideline and as shown here clearly recommends hypocaloric feeding, which means delivering around 70 to 75% of the estimated energy in the first seven days of critical illness and supplying more at a time. And the body is critically ill, is associated with a higher risk of mortality. So knowing all of that, but maybe it is important, I'll pay a bit more attention to all the non caloric, also non nutritional calories, which we are providing in the form of propofol or in the form of citrate. And this is what led certainly these experts here to say that citrates should be included in the nutritional assessment. So my take is where I work, we can't do these complicated, and laborious analyses as they were done at the Mayo Clinic. So we say if our protocol works, then patients get on average 250 kilocalories extra provided the citrate works and grants for 24 hours. And we now do this as we have changed our practice given the latest findings from the nutrition literature.

Speaker 2: 16:27

And then the final metabolic complication I'd like to talk about briefly is the potential effect on bone metabolism. And the reason I mentioned this now is because when I tried to introduce citrate in our unit, I was working with clinicians who were, established fantastic nephrologists, but they were very worried about bone because progress dealing with end stage renal failure. This is what you're worried about clearly. And they were concerned that the citrate would interfere with parathyroid regulation and ultimately worsen renal bone disease. I tried to dismiss all of this, but when I went to the literature, indeed there are case reports and descriptions talking about the risk of osteopenia, the risk of osteoporosis and

fractures in patients who had prolonged CRRT with citrate. Its one of these, there is another one here . And I guess I can show you this where you will immediately see it's actually quite confounding.

Speaker 2: 17:37 It's not straightforward because this was a case report alluding to the potential complication of citrate on bones, But when you look at this case, they say 30 year old man who with with severe multiorgan problems who had CRRT for 254 days during which time he had illnesses and had steroids and was in bed and had severe immobility and all of those may well explain the fact that he subsequently got spontaneous fractures of his lung bones this was, 30 year old man, and he developed severe osteoporosis including the spine and subsequently had a spine fracture. There may be many reasons immobility being one of them and critically ill being an important one, but when they tried to go back and analyze all the results which they had and blood results, what they had collected during clinical practice, it turned out that indeed this man who had acute kidney injury from which she had recovered had severe hyperparathyroidism during this time.

Speaker 2: 18:47 And when you look at the ionized calcium concentration during this time, then they were more or less in the normal range, but not always. There were periods where the ionized calcium concentration was significantly below the normal range. Now is that relevant? Well, for those of you who are interested in renal failure disease and hyperparathyroidism and parathyroid regulation as my colleagues were it probably is because it turns out, we all have a lot of parathyroid hormone sitting in our parathyroid glands. It's all ready to get into action. It's waiting for a signal and the trigger is hypercalcemia, but it's all preformed sitting in the visicus in the parathyroid gland. So as soon as the ionized calcium concentration falls below the normal range, this preform parathyroid hormone gets released within minutes and it's there. And this is a mechanism, a natural God invented this mechanisms so that we would always be protected from hypercalcemia.

Speaker 2: 19:55 So clearly we'd have a parathyroidism. You may well have effects on bone because the parathyroid will once released will immediately quickly activate osteoclast and then has some other effects obviously on the gut. And the kidney to restore calcium. But the key bit is that calcium parathyroid gets released, in response to minute changes in ionized calcium. And secondly, this happens within minutes very, very quickly. It's there to protect us, but it is possible that during citrate based anticoagulation, this could be harmful. So because of these

reports, plus I felt I had to reassure and calm down my colleagues who are quite concerned about this. we looked at the parathyroid levels in patients on citrate. The main reason, was I wanted to assure them that they were unnecessarily worried. So with a protocol we were using, which is, again trisodium citrate and CVV HD and a very strict, training program for the nurses where they are instructed to aim for a ----------e to Ionized calcium concentrations and instructed to keep the systemic ionzed calcium concentration in the normal range.

Speaker 2: 21:23

We then measured PTH of regular levels serially in patients who were on citrate base CRRT for more than three days. And from then on we met at every day. We also looked at other related variable hormones, but the key one is really the PTH. And when we did that, we showed that, indeed physiology works even when you're on citrate based CRRT So as soon as the ionized calcium level dropped, we saw a rise in PTH, turn it the other way round. If we kept the ionized calcium concentration in the serum in the normal range then we saw stable PTH levels and a multivariable analysis where we, evaluated all the various factors which may affect PTH it turned out, that the serum ionized calcium concentration was the highest trigger. All this fits with normal physiology and a fall in the systemic ionized calcium concentration was associated with a very quick increase in PTH. Bringing it back into the normal range resulted in a decrease in PTH. And these associations were independent of magnesium, independent of phosphate levels and independent of various other factors which may affect PTH. So from our single center analysis we could conclude based on our data, that PTH concentrations were maintained, stable, provided the systemic ionized calcium concentration was also stable and safely maintained in the physiologic range.

New Speaker: 23:09

So that's where I want to end. Having mentioned metabolic acidosis, caloric gain and hyperparathyroidism. I wanted to demonstrate that citrate has metabolic effects, can cause metabolic alkalosis as outlined by Professor Legrand, can cause metabolic acidosis and those who cannot metabolize citrate either because they have inadequate muscle and liver capacity, or because they suffer from intracellular hypoxia. I've alluded to the fact that citrate provides energy and contributes to the caloric gain and why is it maybe acceptable for some patients. You have to be sure that it doesn't cause overfeeding, because we now know that overfeeding is associated with an increased risk of dying. And finally, I believe we need to understand much better how these various citrate protocols, work and how they affect potential bone health. I accept that this is something, the bone we have ignored for a long time. Nobody in ICU is worried

about bones, but this is something which then develops later in survivors. These are people who then end up with severe osteoporosis and remain at high risk or at higher risk of bone fractures. And that's where I would like to end. Thank you.